Chapter 2. Methodology

This evidence report is based on a systematic review of the literature. Several teleconferences were held with the science partner representatives from the Social Security Administration (SSA), the American Academy of Pediatrics (AAP), the internal technical experts from the EPC, and a representative of the Disability Law Center to refine and address the key question formulated by SSA. A comprehensive search of the medical literature was conducted to identify the evidence available to address the questions.

Detailed information about each study used in the systematic review was abstracted. The results are presented as detailed evidence tables. Information directly pertinent to answer each aspect of the key question is presented in summary tables with the Results chapter (Chapter 3).

Key Question Addressed in the Evidence Report

Current SSA guidelines consider FTT to be present when there is a fall in weight to below the 3rd percentile or to less than 75% of median weight-for-height or age in children under two years old. There must be no underlying medical disorder, and growth failure should last, or be expected to last, for at least twelve months. Disability is defined as the presence of a 'medically determinable physical or mental impairment' that causes 'marked and severe functional limitations' and that is expected to last for twelve months or more. In turn, a 'medically determinable impairment' is 'an impairment that results from anatomical, physiological, or psychological abnormalities which can be demonstrated by medical evidence consisting of signs, symptoms and laboratory findings' (Disability evaluation under Social Security. Social Security Administration, 1999)

SSA Functional limitations may occur in any of six areas of functioning: 1) acquiring and using information; 2) Attending and completing tasks; 3) Interaction with others; 4) Moving about and manipulating objects; 5) caring for oneself; and 6) health and physical well-being. Marked limitation in two areas or extreme limitation in one suffices to establish disability. These guidelines are to be updated and the purpose of this study question was to generate an evidence base to assist the SSA in revising its disability policy.

Following a series of teleconferences, science partners and EPC technical experts arrived at a consensus on the main study question as outlined below:

- *Among children defined by investigators as failing to thrive or grow adequately, what evidence exists that they have a concurrent disability (or will have one within six months)?*

For the purposes of this question, the SSA definition of disability was applied; however, the definition of FTT was expanded to include growth failure in children older than two years, with failure to grow at the expected rate, without reference to specific percentile height and weight cutoffs or underlying medical conditions. Duration of disability was to be at least six months.

Search Strategies

Disability is not a specific medical condition that can readily be searched for. Thus, we had to look at many studies with related concepts (i.e. medically definable impairments that are related to disability) to identify potentially relevant studies.

The main search consisted of a MEDLINE® search from 1966 through December 2000. A broadly sensitive, rather than specific search strategy was employed to identify relevant studies. The search strategy used the following textwords: failure to thrive, failure to grow, growth retardation, childhood malnutrition, protein-calorie malnutrition, starvation and psychosocial dwarfism. Results were limited to studies in age group under 18 and English language only. We also inspected references from retrieved primary studies, relevant reviews, and consulted with technical experts and colleagues in order to identify additional studies.

A total of 10,486 abstracts were identified in the initial search. An updated MEDLINE® search using the same search strategy was conducted in September 2001, which resulted in additional 480 abstracts.

Study Selection

Physician members of the EPC and pediatricians manually screened titles and abstracts to identify potentially relevant articles. Inclusion criteria for article selection were as follows: 1) published articles including at least one disability-related outcome; 2) cross-sectional or longitudinal studies; 3) studies with at least two arms, one of which had a non-failure to thrive or healthy control group; 4) studies conducted in either developed or developing countries. Studies of sample size of less than 10 subjects per arm or those concerned primarily with particular diagnoses and conditions were excluded, as were studies published only as abstracts. The third inclusion criterion was added to control for potential confounders for any particular statistically significant outcome or covariate.

The mechanisms of undernutrition have been well studied in developing countries. In addition, the associations of undernutrition and various outcomes such as cognitive and neurological development, and infections are clearly delineated in these conditions. Because undernutrition as applied to developed countries may not be understood or studied as extensively, studies in developing countries were included to help correlate associations made.

Covariates / Outcomes Considered

Disability-related concepts include mental or physical impairment that results from anatomical, physiological, or psychological abnormalities that can be shown by medically acceptable clinical and laboratory diagnostic techniques. A physical or mental impairment must be established by medical evidence consisting of signs, symptoms, and laboratory findings. The rational is to relate FTT with physical or mental impairment. There are factors that in turn may cause or modify the severity of the impairments. Listed below are factors or correlates explored in this evidence report.

Table 1. Outcomes and covariates studied

Outcomes	
Social/behavioral functioning	Neurological development
Infectious illnesses	Anthropometric, measurements
Cognitive development	
Covariates	
Perinatal –	Organic illness –
Tobacco	Congenital defects
Alcohol	Pulmonary
Cocaine	Cardiovascular
Infection	Gastrointestinal
Prematurity	Kidney
LBW	Neurological
Demographic –	Immunologic
Education	Infectious
Income	Endocrine
Health coverage	
Maternal IQ	
Quality of HOME Environment	
Age	
Gender	

Data Abstraction

The data abstraction form was developed as part of an iterative process involving the methodologic and domain experts. The form was designed to capture data from primary articles including study setting, demographic data on the study subjects as well as data on the family social-economic status (SES), inclusion/exclusion criteria, number of subjects, study design, funding source, relevant measurements and outcomes evaluated, statistical methodology, results, potential biases, and study quality.

As part of the data abstraction form development, domain experts performed data abstraction after a training period. Each pediatrician tested the form with two different articles and each article was extracted at least twice by different pediatricians. Because of the variation of data reporting by the primary articles, this process also served to validate the forms.

Data abstraction of each study was performed in duplicate, once by the pediatrician and once by an EPC methodologic staff. Discrepancies were resolved in a conference or by a third reviewer.

Reporting the Evidence

The evidence we found for the FTT is summarized in two complementary forms. The evidence tables provide detailed information about the feature of study design and results of all the studies reviewed. A narrative and tabular summary of the strength and quality of the evidence of each study are provided for each main outcome. In addition, the country in which the study was conducted was divided between two sets of tables categorized by developed and developing

countries. This is for the purpose of generalizability as conditions are more severe in developing countries and may not apply to the FTT populations in the United States. However, the outcomes can provide a parallel comparison to measure the strength of association.

Evidence Tables

Evidence tables were constructed for five different categories and grouped between developed and developing countries. The categories include cognitive & neurological development, behavioral problems, immunologic response or infectious diseases, anthropometrics, and other correlates/outcomes. They are presented under the Evidence Tables section of this evidence report:

Evidence Tables in the Report

Table Number	Table Content
Evidence Table 1	Studies associating anthropometrics with Failure to Thrive patients compared to healthy control subjects in developed countries
Evidence Table 2	Studies associating anthropometrics with malnourished patients compared to well-nourished control subjects in developing countries
Evidence Table 3	Studies associating immunologic response or infectious diseases with Failure to Thrive patients compared to healthy control subjects in developed countries
Evidence Table 4	Studies associating immunologic response or infectious diseases with malnourished patients compared to well-nourished control subjects in developing countries
Evidence Table 5	Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries
Evidence Table 6	Studies associating behavioral problems with malnourished patients compared to healthy control subjects in developing countries
Evidence Table 7	Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries
Evidence Table 8	Studies associating cognitive & neurological development with malnourished patients compared to well-nourished control subjects in developing countries
Evidence Table 9	Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries (miscellaneous)
Evidence Table 10	Studies associating other correlates / outcomes with malnourished patients compared to well-nourished control subjects in developing countries (miscellaneous)

Summary Tables

Summary tables were created to describe studies reviewed for each main topic. The tables describe the strength of the evidence according to six dimensions: study size, age at follow-up, duration of follow-up, study sample applicability, strength of association, and methodological quality. The study data on follow-up duration and age at enrollment were presented in a heterogeneous manner that required reporting of follow-up data to be approximated in some cases. When possible, follow-up time was calculated from the age of diagnoses of FTT or malnutrition. The summary tables are presented in Chapter 3 of this evidence report.

Summarizing the Evidence of Individual Studies

In order to answer the key questions, it was necessary to assess the strength of the available evidence. There is no current standard approach to assess the methodological quality and the reliability of these studies. In this report, we used the evidence-grading scheme described below.

Study Quality

Methodological quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of design types were evaluated, a three-level classification of study quality, used in previous reports, was modified:

- ● Least bias: Results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study; prospective design, clear description of the population and setting; proper measurement techniques; appropriate statistical and analytic methods; no reporting errors; no obvious bias.

- ◉ Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria of category A. It has some deficiencies but none likely to cause major bias.

- ○ Significant bias that may invalidate the results. A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting.

Applicability

Applicability (also known as generalizability or external validity) addresses the issue of whether the study population is sufficiently broad so that the results can be generalized to the population of interest at large. The study population is typically defined by the inclusion and exclusion criteria. The target population was defined to include patients with non-organic failure to thrive, except for studies that included a small subset of FTT deriving from possible or definite organic etiology. A designation for applicability was assigned to each article, according to a three-level scale.

 Patients enrolled in the trial represent a broad spectrum of the population (high degree of applicability). Typically this would be a large study, although a large study in itself does not guarantee a high degree of generalizability.

 The study included only a narrow/restricted study population, but the result is relevant to similar types of patient population (restricted applicability). Typically this would be a small study, but may also be a large study of a very homogeneous population.

 Studied outlier population that is not immediately relevant to the study question (very limited direct applicability or not applicable), or where the study reported only limited information.

Results

Results are represented by proportions (percents), categorical variables, mean levels for continuous variables, and associations between study measures and children with FTT compared to children without FTT. Symbols indicate the type and significance of associations between study measures.

⬇ or ⬆ Statistically significant association, ($p < .05$)

⇧ Positive association

⇔ No association

⇩ Negative association or inverse relationship

Study Size

The study size is used as a measure of the weight of the evidence. Some studies have a high drop out rate due to lost to follow-up; we provide both the enrolled and evaluable number of patients, when these data are reported. A large study provides a more precise estimation of the treatment effect but does not automatically confer broad applicability unless the study included a broad spectrum of patients. Very small studies, taken individually, cannot achieve broad applicability. But several small studies that enrolled diverse populations, taken together, may have broad applicability. The study size is included as a separate dimension used to assist the assessment of applicability. For summarizing all studies, this would be the number of studies and the total number of patients in these studies.